

# Procalcitonin for individualizing antibiotic treatment: an update with a focus on COVID-19

Selina Wolfisberg<sup>a</sup>, Claudia Gregoriano<sup>a</sup> and Philipp Schuetz<sup>a,b</sup>

<sup>a</sup>Department of Medicine, Kantonsspital Aarau, Aarau, Switzerland; <sup>b</sup>Medical Faculty, University of Basel, Basel, Switzerland

## ABSTRACT

Procalcitonin (PCT) is useful for differentiating between viral and bacterial infections and for reducing the unnecessary use of antibiotics. As the rise of antimicrobial resistance reaches “alarming” levels according to the World Health Organization, the importance of using biomarkers, such as PCT to limit unnecessary antibiotic exposure has further increased. Randomized trials in patients with respiratory tract infections have shown that PCT has prognostic implications and its use, embedded in stewardship protocols, leads to reductions in the use of antibiotics in different clinical settings without compromising clinical outcomes. However, available data are heterogeneous and recent trials found no significant benefit. Still, from these trials, we have learned several key considerations for the optimal use of PCT, which depend on the clinical setting, severity of presentation, and pretest probability for bacterial infection. For patients with respiratory infections and sepsis, PCT can be used to determine whether to initiate antimicrobial therapy in low-risk settings and, together with clinical data, whether to discontinue antimicrobial therapy in certain high-risk settings. There is also increasing evidence regarding PCT-guided therapy in patients with coronavirus disease 2019 (COVID-19). This review provides an up-to-date overview of the use of PCT in different clinical settings and diseases, including a discussion about its potential to improve the care of patients with COVID-19.

**Abbreviations:** CAP: community-acquired pneumonia; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; DIC: disseminated intravascular coagulation; ED: emergency department; ECOPD: exacerbated chronic obstructive pulmonary disease; HAP: hospital-acquired pneumonia; ICU: intensive care unit; LOS: length of stay; MR-proADM: mid-regional pro-adrenomedullin; PCT: procalcitonin; SOFA: sequential organ failure assessment; SARS-CoV-2: severe acute respiratory syndrome coronavirus type 2; VAP: ventilator-associated pneumonia; WHO: World Health Organization

## ARTICLE HISTORY

Received 1 July 2021  
Revised 10 August 2021  
Accepted 30 August 2021

## KEYWORDS

Antimicrobial stewardship; biomarker; COVID-19; procalcitonin

## Introduction

Almost ten years after its initial description in humans [1], the possible diagnostic, prognostic, and therapeutic qualities of the biomarker procalcitonin (PCT) were first discussed by Assicot et al. who found a correlation between elevated PCT levels and bacterial infection, with higher levels in severe cases as well as decreasing levels of PCT under antibiotic therapy [2]. PCT is the 116-amino-acid precursor of calcitonin [1], which is synthesized in the C cells of the thyroid in healthy individuals [3], resulting in PCT levels  $<0.1 \mu\text{g/L}$  [4]. In cases of bacterial infection, PCT is produced ubiquitously by organs, such as the lung, liver, kidney, brain, pancreas, small intestine, and heart with values increasing up to 1000-fold, as has been shown in experiments with animals [3]. A few hours after stimulation through

endotoxins, including interleukin-1 (IL-1) and interleukin-6 (IL-6) or tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), PCT levels start to rise and reach their peak at around 12 to 24 h and can persist for several days [4–6]. Other conditions that may also lead to increased PCT levels are other systemic infections (e.g. fungal-, parasitic-, but not autoimmune-mediated inflammation) [5,7,8], trauma [9], major surgery [10], severe burns [11], liver cirrhosis [12], acute pancreatitis [13], or aspiration pneumonitis [14], and they are physiologically increased in neonates during their first days of life [15,16]. Elevated PCT levels have also been found in patients with renal dysfunction [5].

In contrast, the expression of *CALC-I*, the gene responsible for calcitonin synthesis, was shown to be suppressed in viral infections through the release of cytokines, such as interferon- $\gamma$ , leading to lower levels

of PCT [17]. Thus, PCT has the potential to differentiate between viral and bacterial infections and to improve decisions regarding antibiotic use—a process also known as PCT-guided antibiotic stewardship. To reinforce just how important a more prudent use of antibiotics and antimicrobial stewardship programs are, in 2014, the World Health Organization (WHO) described the rise of antimicrobial resistance as “alarming” and concluded that a time when even minor infections might be fatal again was “a very real possibility for the twenty-first century” [18]. Here, a biomarker-based approach might help to support evidence-based antibiotic use and at the same time reduce risks for side effects from antibiotics.

However, the optimal use of PCT-guided antibiotic therapy has been discussed for a long time [19,20]. Many reviews and meta-analyses concluded that PCT is a good indicator of bacterial infection [21–24] and that overall antibiotics exposure can be reduced safely [25–36]. Some also found improved clinical outcomes, including lower mortality, particularly for discontinuation strategies in critically ill patients [37–42]. In addition, PCT has been discussed as a marker for illness severity, for example, in septic patients [43]. However, several trials concluded that prognostic evaluation of patients should not be based on PCT alone [44,45]. Further controversy persists due to the heterogeneity of trial data [26,46–49] and more recent trials reporting no significant benefits of PCT [26,50,51]. These differing results may be due to different settings, populations, and diseases all needing a specific approach, which makes general statements difficult. This is also reflected in the different cutoff values proposed by an international expert consensus paper in 2019 [52]. Therein, antibiotic therapy was recommended based on clinical assessment and a PCT cutoff value of  $\geq 0.25 \mu\text{g/L}$  for patients with mild to moderate illness and  $\geq 0.5 \mu\text{g/L}$  for patients admitted to the intensive care unit (ICU) [52]. The consensus further recommended serial PCT measurements to reevaluate the need for antibiotics as well as to consider reduction of  $>80\%$  of peak PCT values as a strong indicator for early discontinuation of antibiotics [52].

This review will discuss established PCT use in light of the most recent knowledge for different settings and different diseases. The PCT-based approach for the treatment and management of patients suffering from the novel coronavirus disease 2019 (COVID-19) will be particularly emphasized.

### Primary care and general practice

Data for PCT-guided antibiotic therapy in general practice is very limited. A Cochrane overview of systematic

reviews from 2017 found one review that investigated the use of PCT in a primary care setting, based on only two trials [53]. Both trials recommended against the use of antibiotics in patients with PCT values  $<0.25 \mu\text{g/L}$  and suggested reassessing patients without clinical improvement within 24–48 h [34]. The Cochrane review concluded that PCT guidance reduced antibiotic prescription in acute upper and lower respiratory infections without impairing patient outcomes, attesting the available evidence moderate quality [53]. However, similar results were also demonstrated for the use of C-reactive protein (CRP) testing, though CRP differentiates between viral and bacterial infections less accurately [53,54]. They further noted that the overall effect, that is, the reduction in an antibiotic prescription, was small but “likely to be clinically important” [53].

Acute rhinosinusitis, another condition often encountered by general practitioners, was the subject of a systematic review published in 2019 [55]. Based on two randomized controlled trials, the review concluded that PCT-guided therapy was able to significantly reduce antibiotic use without negatively affecting patient outcomes, for example, impaired activity or missed workdays [55]. However, the authors caution that data are very limited and, in this case, based on only 245 patients in total [55].

For lower respiratory tract infections, more evidence is expected to emerge soon, as an ongoing randomized trial compares PCT testing to lung ultrasonography and standard of care in patients with suspected pneumonia in a general practice setting [56].

### Emergency department (ED)

A systematic review of prospective trials found that PCT-guided therapy in the emergency department (ED) was safe and effective [57]. However, most of these trials focused on adult patients with respiratory infections, thus limiting generalizability to other patient populations [57]. In addition, protocol non-adherence was identified as one of the main issues in these trials [57].

After the review was published, another trial looked at a broad population of emergency patients by studying PCT management in patients with fever (HiTEMP study) [50]. Compared to the control group, they found non-inferiority of PCT-guided therapy regarding safety but no reduction in the number of patients who received antibiotic treatment and overall low accuracy for the diagnosis of infections, specifically lower than CRP [50]. In contrast, most previously published studies have reported otherwise, and two Cochrane reviews from 2017 found significantly lower exposure to

antibiotics in patients admitted to the ED with lower respiratory infections [41,53]. The higher cutoff value for PCT ( $\geq 0.5 \mu\text{g/L}$ ), the heterogeneous study population, and low protocol adherence (66%) in the HiTEMP study may explain these differing results [50]. However, another clinical trial included only patients with acute lower respiratory tract infection, used a lower cutoff value for PCT ( $\geq 0.25 \mu\text{g/L}$ ), reported a higher protocol adherence (73%), and still failed to find a significant reduction in antibiotic exposure [51]. Due to these differing recent results, more research and reappraisal of the use of PCT in different subgroups are required to determine which ED population benefits the most from PCT-guided therapy.

### Medical ward

For hospitalized patients, serial PCT measurements are superior to single measurements regarding the prognostic value and monitoring of therapeutic success [4,16,58–61]. Specifically, discontinuation of antibiotics based on a reduction of PCT to 80% of its peak value has been tested in different settings, including medical, pediatric, and intensive care patients [4,37,58,61–63]. Again, most trials focused on respiratory diseases. However, different diagnoses require specific approaches to PCT-guided therapy, some of which, including COVID-19, will be discussed in the following paragraphs.

### Community-acquired pneumonia

Two meta-analyses based on largely the same trials between 2006 and 2011, most of which used a PCT cutoff of  $0.25 \mu\text{g/L}$ , found initiation, duration, and total exposure of antibiotics to be significantly reduced in PCT-guided therapy for patients with community-acquired pneumonia (CAP) [40,41]. However, they also reported high levels of interaction, suggesting subgroup differences, and neither analysis found a significant reduction in mortality [40,41]. In addition, a systematic review found that PCT is better as a prognostic than as a diagnostic tool for CAP [64], and a recent meta-analysis reported that a PCT cutoff of  $0.5 \mu\text{g/L}$  yielded low sensitivity and medium specificity, concluding that the biomarker should not be used to decide whether to initiate or discontinue antibiotic treatment [65]. These conclusions are further supported by more recent trials that failed to find a reduction of antibiotic use [51,66], and one study reported PCT to be outperformed by CRP and IL-6 regarding diagnostic accuracy for pneumonia in patients presenting with

dyspnea [67]. These differing results may be explained by several factors, including low adherence and lower exposure in the control group due to changes in clinical practice, such as the establishment of short-course therapy [68]. Furthermore, CRP has been shown to differentiate between bacterial and viral infections less accurately than PCT [54], and the long turn-around time of IL-6 limits its use in clinical practice. It remains to be seen whether future trials will confirm these results.

### Hospital-acquired and ventilator-associated pneumonia (HAP/VAP)

Two different guidelines for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are currently in use, one by the Infectious Diseases Society of America and the American Thoracic Society [69] and the other by a group of European and Latin American societies [70]. They recommend against the routine use of PCT for decisions regarding the initiation of antibiotics in these populations [69] and as a predictor for the patient outcome or measurement for treatment success [69,70]. However, both acknowledge the usefulness of PCT as an additional tool to clinical assessment to discontinue antibiotics, although the quality of evidence is lacking and further studies are needed [69,70].

### Chronic obstructive pulmonary disease (COPD)

Several trials have investigated the use of PCT in patients with exacerbated chronic obstructive pulmonary disease (ECOPD), most of which used a  $0.25 \mu\text{g/L}$  PCT cutoff. Two meta-analyses summarizing trials from 2007 to 2016 found initiation, duration, and total exposure of antibiotics were significantly reduced in PCT-guided therapy patients compared to control group patients, without negative effects on outcomes [40,41]. However, they also reported high levels of interaction for some of their data, suggesting subgroup differences and neither analysis found a significant reduction in mortality [40,41]. Another meta-analysis from 2017 with a slightly different selection of trials also found a significant reduction of antibiotic exposure without a significant effect on mortality, length of stay (LOS), or treatment failure [28]. The significantly lower use of antibiotics was further confirmed by a meta-analysis conducted in 2020, which included trials until 2018 [71]. However, the authors did not support the use of PCT-guided therapy for ECOPD as the effect on antibiotic duration disappeared when trials with a high risk

for bias were excluded [71]. Thus, despite the general agreement that PCT-guided therapy can reduce antibiotic use, the quality, bias, and heterogeneity of the available evidence are insufficient and further research is needed, particularly for determining optimal cutoff values or comparing PCT to CRP [26–28,72].

### **Coronavirus disease 2019 (COVID-19)**

During the current pandemic, there has been much interest in using PCT for managing patients with COVID-19, caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and first described in China in 2019 [73,74]. Patients with COVID-19 often present with unspecific symptoms also common in other respiratory diseases, making differentiation from bacterial infection challenging. Thus, the value of biomarkers, such as PCT and their diagnostic, prognostic, and therapeutic qualities were reassessed in light of the current pandemic. An overview of recent trials can be found in Table 1.

Based on a Cochrane meta-analysis from November 2020, routine laboratory testing, including PCT, has low sensitivity ranging from 0 to 48% and specificity from 26 to 95% to diagnose COVID-19 [75]. However, the authors also noted that certainty for their estimates was low to very low [75]. More recently, an Italian study also concluded that PCT did not help to distinguish between COVID-19 and other respiratory or febrile illnesses in a small observational study [76].

On the other hand, numerous studies reported that PCT levels correlated significantly with the severity of disease, complications, and clinical outcome of COVID-19 [77–92]. While initial analyses assumed that high PCT was a sign for bacterial superinfection [22] and high antibiotic administration [93,94], the rate of bacterial coinfection in COVID-19 patients has been shown to be as low as 7% [95], with higher rates among patients admitted to the ICU [95–97]. These numbers are significantly lower compared to patients with influenza, where bacterial infections were more frequent and a relevant cause of mortality [95]. Furthermore, PCT levels were also lower than those of pneumonia patients [76,98]. Thus, it is not yet clear whether PCT can be used as a marker of bacterial coinfection for COVID-19 patients in the same way it has been used in other respiratory diseases.

There are also recent data suggesting that PCT ( $>0.5 \mu\text{g/L}$ ) could be an important prognostic indicator for hyperinflammation and the cytokine storm typically seen in severe COVID-19 progression [99]. Identification of patients at risk for disease progression may help to

initiate anti-inflammatory medication early, thus reducing viral load and avoiding hyperactivation of the immune system [99]. In addition, a small Turkish study found higher PCT levels in severe COVID-19 patients with disseminated intravascular coagulation (DIC) [100]. The therapeutic consequences of elevated PCT levels should thus not only focus on antibiotic administration but also other treatment requirements.

During the COVID-19 pandemic, antibiotic overuse has become an important issue because patients often present with high severity of illness and high inflammation, and diagnosing bacterial superinfection in such a situation is challenging. The pandemic thus reduced the success of already established antimicrobial stewardship programs, for example, in the United Kingdom with more physicians using antibiotics despite the absence of bacterial infection [101]. Thus, the implementation and expansion of these programs have become even more important. Most of the studies investigating the usefulness of PCT-guided therapy in COVID-19 patients found reduced antibiotic use with no negative impact on outcomes [102–105]. However, study designs were observational and heterogeneous with small sample sizes, making strong conclusions difficult to draw. Further research is needed to determine the role of PCT in antimicrobial stewardship programs targeting COVID-19 patients.

### **Other types of infections and settings**

There are several other areas where PCT may be useful, including meningitis [106,107], urinary tract infections [108], chronic heart failure [109–111], and acute asthma exacerbation [112]. Overall, PCT has shown promising results, though the lack of high-quality data does not allow for decisive conclusions or recommendations yet. Similarly, studies in low-income countries, where availability and relative cost of PCT testing may differ, report encouraging results, but these findings are also based on little data [113,114].

Other research areas where more data is needed concerning PCT-guided therapy are in immunosuppressed patients and those with neutropenia, two populations that have been excluded in most trials. However, there are two ongoing trials studying patients treated with anti-IL-6 therapy and patients with chemotherapy-induced febrile neutropenia, respectively, which will hopefully advance the field further (INTER-ACT, ClinicalTrials.gov identifier: NCT04281602c; CALIF, ClinicalTrials.gov identifier: NCT03182465).

**Table 1.** Overview of discussed COVID-19 studies, including population descriptions, outcomes, and conclusions.

Reference	Place, time of data collection	Design	No. of patients	Severity	Cutoff	Outcome(s)	Conclusion
Zhou et al.	China, Dec 2019–Feb 2020	n.a.	70 COVID-19, 70 CAP	All	n.a.	COVID-19 compared to CAP	PCT higher in COVID-19
Bacterial coinfection, mortality Vaughn et al.	United States, Mar–Jun 2020	Retrospective	1705	All	>0.5 µg/L, <0.1 µg/L	Bacterial coinfection	Positive predictive value 9.3%, Negative predictive value 98.3%
Dolci et al.	Italy, Feb–Mar 2020	Retrospective	83	All	(1) <0.25 µg/L (2) >6.7 µg/L	Bacterial coinfection, mortality	Bacterial infection: (1) 92% negative predictive value, 93% sensitivity Mortality: (2) 92% positive predictive value, 27% sensitivity
Van Berkel et al.	Netherlands, n.a.	n.a.	66	Severe (ICU)	>1 µg/L, <0.25 µg/L	Bacterial coinfection	Positive predictive value 93%, Negative predictive value 81%
Vanhomwegen et al.	Belgium, Mar–Jun 2020	Retrospective	66	Severe (ICU)	(1) >0.5 µg/L (2) >2.5 µg/L	Bacterial coinfection (within 48 h after ICU admission), 30 days mortality	Bacterial infection: (1) 80% sensitivity, 48% specificity; (2) 65% sensitivity, 85% specificity Mortality: 0.77 AUC
Antibiotic prescription, exposure Peters et al.	United Kingdom, Apr 2020	Retrospective	118	Low/moderate (no ICU)	<0.25 µg/L	AB prescribed or stopped within 48 h	AB never started or stopped within 48 h in 72%
Pulia et al.	United States, Mar–May 2020	Retrospective	73	All	>0.25 µg/L	AB prescription	Reduced AB prescription in high PCT group
Williams et al.	United Kingdom, Mar–Apr 2020	Retrospective	368	All	≤0.25 µg/L	AB prescription, mortality, ICU admission	Reduced AB prescription (without increasing mortality); higher mortality and ICU admittance in high PCT group
Heesom et al.	United Kingdom, Apr–May 2020	Prospective	52	Severe (ICU)	>0.5 µg/L	AB duration, ICU LOS	AB duration and ICU LOS longer in high PCT group
Other outcomes Garrido et al.	Spain, Mar–May 2020	Retrospective	56	All	n.a.	ICU admission, mortality	PCT higher in patients admitted to ICU and non-survivors
Asoğlu et al.	Turkey, Apr–Jun 2020	Retrospective	71	Severe (ICU)	n.a.	DIC	PCT higher in patients with DIC
Krause et al.	United States, Mar–Apr 2020	Mixed (retrospective and prospective)	93	Severe (invasive mechanical ventilation)	>0.1 µg/L	Intubation duration, 28 days mortality	Intubation duration longer in high PCT group, no difference in mortality

AB: antibiotics; AUC: area under the curve; CAP: community-acquired pneumonia; COVID-19: coronavirus disease 2019; DIC: disseminated intravascular coagulation; ICU: intensive care unit; LOS: length of stay; n.a.: not available; PCT: procalcitonin.  
Sorted by outcome and severity.

## Intensive care unit (ICU)

For critically ill patients with suspected infection, PCT has little opportunity to change initial antibiotic management but is recommended to help individualize and shorten treatment duration during the course of disease [4]. Two recent trials from France and the Netherlands tested PCT in a critical care setting [37,115]. The latter investigated a general ICU population based on a prospective, multicenter design and found both reduced antibiotic use and lower mortality in the PCT-guided group [37]. The French researchers, on the other hand, conducted a non-inferiority trial investigating patients with ECOPD, finding not only similar antibiotic use in their groups but also significantly higher mortality among PCT-guided patients [115].

Nevertheless, several recent meta-analyses found PCT-guided therapy to reduce antibiotic use when used for early discontinuation [20,36,39,116]. The benefit for mortality, however, was not reported in all studies. They also noted that methodologies and data regarding the use of PCT were very heterogeneous and meta-analyses might thus misrepresent its utility [117], resulting in evidence of low certainty and with a high risk of bias [39]. Furthermore, the reported survival benefit “occurred primarily in studies with low protocol adherence and studies with algorithms combining PCT with other biomarkers” and did not persist when excluding industry-sponsored trials [39]. Similarly, others found reduced mortality but only in discontinuation of PCT-algorithms [20,116] and not in trials with high protocol adherence or patients with high sequential organ failure assessment (SOFA) scores [20], whereas one meta-analysis reported no reduction in mortality at all [36]. Thus, more research is needed to determine whether PCT helps reduce mortality in an intensive care setting.

## Sepsis

Sepsis is a complex condition that requires intensive care and timely intervention. Regarding PCT-guided therapy, the international guidelines of the Surviving Sepsis Campaign issued a weak recommendation for using PCT as a supportive tool to shorten antimicrobial therapy in patients with suspected sepsis, based on what they called low-quality evidence [118]. More recently, two meta-analyses from 2018 found reduced antibiotic use in PCT groups of 1.2 and 1.5 days, respectively, but came to different conclusions regarding mortality [42,119]. While one did not find an effect on either mortality or LOS [119], the other reported significantly lower mortality across different types of

infections (respiratory, urinary, abdominal, etc.) [42]. Similarly, two recent trials from Greece and South Korea found a reduction in antibiotic use of up to 5 days but only the larger Greek study found a reduction in mortality [62,120]. Despite the heterogeneity of the data, overall results suggest that PCT is a good and safe complementary tool to discontinue antibiotics in sepsis, thus reducing antibiotic exposure, while its possible positive effect on mortality requires further research [47,121].

## Department of surgery

PCT has been shown to be elevated in surgery patients, including those with severe trauma [9,122], severe burns [11,122], major surgery [10], liver cirrhosis [12], acute pancreatitis [13], or aspiration pneumonitis [14]. Levels may increase even more in case of complications, such as sepsis [122]. A recent guideline by the World Society of Emergency Surgery included PCT in their recommendations for the management of severe acute pancreatitis [13]. According to them, PCT should be used to 1) detect pancreatic infection, as it is the most sensitive laboratory test available, and 2) assess the risk of infected pancreatic necrosis, as PCT is a strong negative predictor of this outcome [13].

PCT has also been investigated as a potential diagnostic and prognostic marker for infections and outcomes after heart [123] and liver [124] transplantation, aortic [125,126], and other types of cardiac surgery [127], as well as a hip replacement [128]. For other types of infections, the use of PCT has not been thoroughly investigated and recommended. For example, a systematic review recently discussed the role of PCT in periprosthetic joint infections, recommending against the use of PCT as a diagnostic tool to rule out infection [129], and a retrospective study of patients with chronic osteomyelitis came to a similar conclusion [130].

In sum, the role of PCT in a surgical setting is complex and data are controversial, requiring further research to understand the importance and optimal use of PCT in this setting.

## Department of pediatrics

In children, PCT values vary depending not only on the factors discussed above but also on ones that are unique to the pediatric setting, such as gestational age or birth weight [16]. Furthermore, a physiological increase of PCT occurs in the first days of life with different courses for the term and preterm neonates [15,131,132]. The mode of delivery, on the other hand,

influences PCT less than CRP, making PCT a more reliable marker for postnatal sepsis [16].

Two analyses found PCT to accurately diagnose neonatal sepsis but also noted pronounced statistical heterogeneity in the analyzed data without being able to issue a clinical recommendation based on the data available [49,133]. More recently, the multicenter, randomized controlled NeoPIns trial showed PCT-guided therapy to be superior to standard care regarding the reduction of antibiotic use [35]. A secondary analysis of the same data concluded that serial measurements were able to exclude early-onset sepsis with high probability [134].

Much like for adults, sepsis is one of the most researched conditions for the use of PCT-guided antibiotic therapy in children. Other potential diseases include bacterial infection [135], where a recent review reported reduced antibiotic exposure and length of ICU stay [136], as well as bronchiolitis [137] and meningitis [107], all of which showed promising results.

### Limitations and drawbacks of PCT

In addition to the specific drawbacks already mentioned above, there are also more general limitations to consider regarding the use of PCT in guiding antibiotic therapy and the interpretation of trial results.

First, different cutoff values and strategies, such as initiation vs. discontinuation of antibiotics, are necessary for different settings and diseases and depend on their severity. Thus, PCT recommendations need to be individualized based on patient comorbidities, for example, renal dysfunction. Second, the benefits of PCT-guided therapy may depend on health staff education and implementation. Physicians who have had little previous experience with PCT might be reluctant to adjust treatment based on laboratory results, leading to low protocol adherence. Similarly, high adherence might indicate high levels of trust in a test that physicians are already familiar with and use routinely, thus explaining differences among trial results regarding adherence and clinical benefits [20,39]. In addition, the presence of antimicrobial stewardship programs may lower the potential effect of PCT-guided therapy as compared to settings where few other systems are established to reduce the unnecessary use of antibiotics [138]. Also, the assays used to determine PCT levels differ in sensitivity and their performance varies for different settings, infections, and cutoffs, increasing the heterogeneity of trial data [139]. Assay utilization requires not only technical knowledge of their characteristics but also careful consideration of the clinical

setting [139]. Furthermore, the relatively high cost of diagnostics and required infrastructure limits the use of PCT, particularly in low-income countries [113]. The role of industry sponsorship has also been discussed critically as some data suggest that industry-sponsored trials had better results than those without [39]. Finally, there are other emerging markers, such as mid-regional proadrenomedullin (MR-proADM) or presepsin, which may further improve the diagnostic and prognostic assessment of patients.

### Conclusion

There is an increasing need to improve diagnosis and prognosis in patients with different types of infection. The host-derived biomarker PCT has been investigated in a large number of studies from different populations and settings, with sometimes contradictory conclusions. These discrepant findings may be due to several factors, including different cutoff values and strategies (e.g. initiation vs. discontinuation of antibiotics), routine implementation of PCT-guided therapy, protocol adherence, the use of different assays, or the presence of antimicrobial stewardship programs. There is a need for further research on the optimal way to use PCT alone and in conjunction with other emerging markers and diagnostic tools to improve the management of patients with infections.

### Disclosure statement

Philipp Schuetz received support (paid to his employer) and research funding from bioMérieux SA, Thermo Fisher Scientific, Roche, Siemens, and Abbott for attending meetings and fulfilling speaking engagements. All other authors report no declarations of interest.

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